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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/559,383
Filing Date: December 06, 2005
Appellant(s): DIETZEL ET AL.

Mr. Sheldon M. McGee, Esq.
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 12, 2011 appealing from the Office action mailed October 13, 2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-4 and 6-11 are pending and all pending claims are rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

5,795,564	Aberg et al.	08-1998
US 2002/0030068	Burt	03-2002
5,482,934	Calatayud et al.	01-1996
5,474,759	Fassberg et al.	12-1995
WO 01/78738	Gave, Brian	10-2001
WO 00/07567	Keller et al.	02-2000
6,475,467	Keller et al.	11-2002
7,879,833	Weimar et al.	02-2011

García-Marcos et al., "Inhaled corticosteroids plus long-acting beta-2 agonists as combined therapy in asthma," *Expert Opin. Pharmacother.*, **April 2003**, *4(1)*, pp 23-39.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A. Claim Rejections Under 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Appellant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Appellant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

(I) Claims 1, 3-4, 6, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aberg et al. (U.S. Patent No. 5,795,564) (IDS) in view of Burt (US 2002/0030068), García-Marcos et al. ("Inhaled corticosteroids plus long-acting beta2-agonists as combined therapy in asthma," *Expert Opin. Pharmacother.*, April 2003, *4(1)*, pp 23-39) ("García"), and Calatayud et al. (U.S. Patent No. 5,482,934) (IDS).

Appellant Claims

Appellants claim a pharmaceutical suspension formulation comprising (i) the active particles of ciclesonide, physiologically functional derivative, solvate, or salt thereof, (ii) particles of formoterol, salt, , physiologically functional derivative, fumarate dihydrate thereof, or solvate thereof, (iii) HFA 134a (i.e. 1,1,1,2-tetrafluoroethane), HFA 227 (i.e. 1,1,1,2,3,3,3-heptafluoropropane), or mixtures thereof, and (iv) optionally surfactant, wherein in some embodiments the surfactant is oleic acid present in an amount ranging from about 0.001-0.1% w/w and other embodiments, wherein the compositions also comprise disodium cromoglycate at a concentration that is not therapeutically or prophylactically effective (i.e. disodium cromoglycate in claim 10 is not considered an active agent) and the only active agents in the compositions in a therapeutically/prophylactically effective amount or R,R,-formoterol and ciclesonide.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Aberg exemplifies a metered dose inhaler containing a suspension formulation comprising (i) R,R-formoterol fumarate dihydrate, (ii) trichloromonofluoromethane (propellant), (iii) dichlorodifluoromethane (propellant), and (iv) sorbitan trioleate (surfactant) (Example 12: col. 13, lines 3-20). Aberg teaches that commercially available formoterol is a racemic mixture of the "R,R" and the "S,S" enantiomers and is used as a bronchodilator in the treatment of respiratory diseases, such as asthma (col. 1, lines 53-55; col. 2, line 63 through col. 3, line 52; col. 5, lines 11-15, and col. 6, lines 45-50). Aberg teaches that utilizing (R,R)-formoterol is desirable due to its diminished adverse effects, decreased development of tolerance, and increased bronchial distribution upon inhalation administration when compared to racemic formoterol (col. 8, lines 5-10). Aberg teaches that (R,R)-formoterol may be used in combination with other therapeutic ingredients and may be formulated into various forms such as suspensions, which may be administered by inhalation (col. 10, lines 36-60; Example 12: col. 13, lines 3-20; claims 1-3 and 8-12).

Burt teaches that chlorofluorocarbon propellants are being phased out in pharmaceutical formulations, because these propellants deplete the ozone layer [0002] and that suitable alternative propellants include HFA-134a (1,1,1,2-tetrafluoroethane) and HFA-227 (1,1,1,2,3,3,3-heptafluoropropane). Burt identifies several active agents that may be formulated into pharmaceutical compositions in the form of a solution or a suspension in combination with HFA propellants, such as anti-inflammatories (e.g. budesonide, fluticasone, flunisolide, etc.) and bronchodilators (e.g. formoterol) [0016]. Burt explicitly suggests the combination of a long-

acting beta-2 agonist (i.e. salmeterol xinafoate) and an anti-inflammatory steroid (i.e. fluticasone propionate) [0017] in the same pharmaceutical aerosol formulation.

García teaches that data for the combination of a long-acting beta-2 agonist (e.g. formoterol or salmeterol) with an inhaled corticosteroid (ICS) in the same inhaler is as effective as administration of a much higher dosage of the ICS alone for the control of asthma in patients with asthma that is not well controlled with ICS alone (abstract; pgs. 23-24, introduction; pg. 34, section 12; and pg. 34-35 1st paragraph of section 13 and last paragraph of section 13) and permits a decreased likelihood of a patient experience side effects from the ICS. Several studies concerning the effectiveness of the combination of formoterol and budesonide in the treatment of asthma are reviewed in section 2.2. García teaches that the formoterol/budesonide combination was found to improve lung function and asthma control when combined with both low and high doses of budesonide in comparison to asthmatics administered only budesonide (pg. 27, left column, paragraph bridging pages 26-27).

Calatayud teaches the syntheses, purification, and isolation of ciclesonide and that ciclesonide is desirable for the treatment of inflammatory conditions, because it has a greater therapeutic index (i.e. a much lower systemic effects and its effects are more localized) than other commonly administered anti-inflammatory steroids (e.g. budesonide, beclomethasone dipropionate, betamethasone valerate, flunisolide, etc.) (Abstract; col. 1, lines 64-67; Example VII: col. 10, lines 1-44; Table II, compound 7: columns 17-18; Table III, compound 7 under columns 17-18).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Aberg lacks the teaching of compositions comprising formoterol in combination with ciclesonide. This deficiency is cured by the teachings of (Garcia, Burt, and Calatayud). Aberg lacks the teaching of suspension aerosol formulations comprising HFA-134a and/or HFA 227. This deficiency is cured by the teachings of Burt.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Appellants' invention to combine the teachings of Aberg and García, Burt, and Calatayud, because Aberg teaches that (R,R)-formoterol, a long-acting beta2-agonist (LABA), may be combined with other therapeutic agents, and the combination of LABAs with inhaled corticosteroids has been demonstrated to be clinically effective and desirable. An ordinary skilled artisan would have been motivated to combine the teachings of the cited references, because these references all described formulations for the treatment of inflammatory diseases (e.g. asthma). An ordinary skilled artisan would have been motivated to combine (R,R)-formoterol with ciclesonide in lieu of other known inhalable corticosteroids, because ciclesonide has a much greater therapeutic index (i.e. lower systemic effects vis-à-vis its localized therapeutic effects). An ordinary skilled artisan would have been motivated to substitute the chlorofluorocarbon propellants present in Aberg's exemplified suspension aerosol formulation for HFA-134a, HFA 227, or combinations thereof, because CFC's are being phased out in pharmaceutical formulations, due to the damage that CFC's do to the ozone layer, and HFA-134a and HFA 227 are art-recognized as suitable

pharmaceutically acceptable propellants for use in lieu of CFC's. Thus, an ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide with HFA-134a, HFA 227, or combinations thereof.

Regarding the presence of ethanol in amounts less than 3%, none of the prior art references suggest or teach formulations comprising ethanol, thus, meeting this claim limitation. Regarding the number of times a day the claimed formulation is administered, this is an intended use of the claimed composition and does not change the composition claimed. Thus, this limitation is given little patentable weight and is met by the prior art teachings suggesting the composition of claim 1. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(II) Claims 2 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aberg et al. (U.S. Patent No. 5,795,564) (IDS) in view of Burt (US 2002/0030068), García-Marcos et al. ("Inhaled corticosteroids plus long-acting beta2-agonists as combined therapy in asthma," *Expert Opin. Pharmacother.*, April 2003, *4(1)*, pp 23-39) ("García"), and Calatayud et al. (U.S. Patent No. 5,482,934) (IDS) as applied to claims 1, 3-4, 6, 9, and 11 above, and further in view of Fassberg et al. (U.S. Patent No. 5,474,759).

Appellant Claims

Appellants claim a composition as described above, comprising a surfactant and in some embodiments the claimed composition may comprise ethanol.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Aberg, Garcia, Burt, and Calatayud are set forth above.

Fassberg teaches pharmaceutical aerosol formulations comprising (i) a medicament in an amount from 0.01-1% w/w, (ii) surfactant in an amount of 0-3% w/w; (iii) excipient (e.g. ethanol) in an amount from 0-75% w/w, and (iv) 1,1,1,2,3,3,3-heptafluoropropane (HFC 227) (propellant), which was used in lieu of CFC propellants that deplete the ozone layer (title; abstract; col. 1, line 40 through col. 2, line 21). Preferred surfactants include oleic acid, sorbitan trioleate, etc. (col. 3, lines 40-55; col. 5, lines 42-46). Surfactants are used to lower the surface and interfacial tension between the medicament and the propellant and may be used in suspension formulations (col. 5, lines 31-35). The excipient facilitates that compatibility of the medicament with the propellant and also lowers the discharge pressure to an acceptable range (col. 4, lines 55-62). Preferred excipients include ethanol (col. 5, lines 4-30). Suitable medicaments are those which are delivered by oral or nasal inhalation and include bronchodilators (e.g. albuterol), anti-inflammatory compounds (e.g. mometasone furoate, disodium chromoglycate, beclomethasone dipropionate, etc.) (col. 6, lines 6-21). Fassberg exemplifies various formulations comprising a beta agonist bronchodilator (i.e. albuterol) (see Example 1-18 in columns7 and 8) as well as formulations comprising anti-inflammatory steroids (see Examples 19-33 in columns 8 and 9).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Aberg lacks the teaching of formulations comprising ethanol and/or a surfactant. This deficiency is cured by the teachings of Fassberg.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Appellants' invention to combine the teachings of Aberg and Fassberg, because both references teach inhalable formulations suitable for the treatment of asthma that can be formulated as aerosol formulations with hydrofluorocarbon propellants. An ordinary skilled artisan would have been motivated to modify the teachings of Aberg to include ethanol and or a surfactant, such as oleic acid, because Fassberg teaches that both ethanol and surfactants can be added to tune the formulation surface tension and facilitate the compatibility of the medicament with the hydrofluorocarbon propellant. An ordinary skilled artisan would have found it prima facie obvious to select ethanol as a possible excipient as well as oleic acid as a possible surfactant, because both ethanol and oleic acid are taught as being a preferred excipient and surfactant, respectively, by Fassberg. Furthermore, it is noted that approximately 1/3 of Fassberg's exemplified compositions contain oleic acid and approximately 1/6 of Fassberg's exemplified compositions contain ethanol. Thus, an ordinary skilled artisan would likely choose both oleic acid and ethanol from the list of preferred excipients and surfactants from which to prepare pharmaceutical aerosol suspension formulations. An ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide containing

ethanol and/or oleic acid, because Fassberg taught that suspension formulations could contain surfactants and/or excipients, such as ethanol.

Regarding the amount of ethanol and oleic acid recited in Appellants' claims, this amount overlaps with the amounts taught as being suitable by Fassberg. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(III) Claims 1, 3, 9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gavin et al. (WO 01/78738) ("Gavin") in view of Calatayud et al. (U.S. Patent No. 5,482,934) (IDS).

Appellant Claims

Appellants' claims have been described above.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Gavin teaches medicinal compositions comprising (R,R)-formoterol and rofleponide (i.e. a corticosteroid) for the treatment of respiratory diseases, such as asthma, preferably in the form of inhalable compositions (title; abstract; pg. 1, lines 29-33; pg. 2, lines 12-17, and pg. 3, lines

11-21). (R,R)-formoterol may be used in the form of its fumarate salt (pg. 4, lines 17-20). The invented compositions may comprise additional therapeutic agents, such as anti-inflammatory agents (e.g. budesonide, beclomethasone dipropionate, triamcinolone acetonide, etc.) or NSAIDS (e.g. sodium cromoglycate) (pg. 6, lines 1-10). Sodium cromoglycate is synonymous with disodium chromoglycate. Inhalable formulations include powders and suspension aerosols delivered from pressurized packs with the use of a propellant, such as 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, or mixtures thereof (pg. 6, line 27 through pg. 7, line 4; Claim 8). The active ingredients in suspension aerosol formulations have a particle size in the range of 1-10 microns, preferably 1-5 microns (Id.). Gavin exemplifies two metered dose inhaler formulations comprising (R,R)-formoterol fumarate, rofleponide, and 1,1,1,2-tetrafluoroethane (pg. 8, lines 5-25).

The teachings of Calatayud are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Gavin lacks the teaching of formulations comprising ciclesonide. This deficiency is cured by the teachings of Calatayud.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Appellants' invention to combine the teachings of Gavin and Calatayud and replace rofleponide in Gavin's formulations with ciclesonide, because Calatayud teaches that ciclesonide has a greater therapeutic index than other

conventional anti-inflammatory corticosteroids. An ordinary skilled artisan would have been motivated to combine the teachings of the cited references, because it is desirable to utilize a corticosteroid with large therapeutic index, such as ciclesonide, to minimize undesirable systemic effects and maximize the desirable local anti-inflammatory effects. An ordinary skilled artisan would have been motivated to utilize HFA-134a, HFA 227, or combinations thereof, because these propellants are taught by Gavin as being suitable for use in pharmaceutical suspension aerosol formulations. Thus, an ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide with HFA-134a, HFA 227, or combinations thereof. Regarding the presence of ethanol in amounts less than 3%, none of the prior art references suggest or teach formulations comprising ethanol, thus, meeting this claim limitation. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(IV) Claims 2, 4 and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gavin et al. (WO 01/78738) ("Gavin") in view of Calatayud et al. (U.S. Patent No. 5,482,934) (IDS) as applied to claims 1, 3, 9, and 11 above, and further in view of Fassberg et al. (U.S. Patent No. 5,474,759).

Appellant Claims

Appellants claim a composition as described above, comprising a surfactant and in some embodiments the claimed composition may comprise ethanol.

NOTE: The recited intended use of the claimed composition of claim 11 is given little patentable weight, because it does not affect the components of the claimed composition.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Gavin's teachings are set forth above. The teachings of Calatayud are set forth above.

Fassberg teachings are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Gavin lacks the teaching of formulations comprising ethanol and/or a surfactant. This deficiency is cured by the teachings of Fassberg.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Appellants' invention to combine the teachings of Gavin and Fassberg, because both references teach inhalable formulations comprising anti-inflammatory steroids that can be formulated as aerosols suspensions with hydrofluorocarbon propellants. An ordinary skilled artisan would have been motivated to modify the teachings of Gavin to include ethanol and or a surfactant, such as oleic acid, because Fassberg teaches that both ethanol and surfactants can be added to tune the formulation surface

tension and facilitate the compatibility of the medicament with the hydrofluorocarbon propellant. An ordinary skilled artisan would have found it prima facie obvious to select ethanol as a possible excipient as well as oleic acid as a possible surfactant, because both ethanol and oleic acid are taught as being a preferred excipient and surfactant, respectively, by Fassberg. Furthermore, it is noted that approximately 1/3 of Fassberg's exemplified compositions contain oleic acid and approximately 1/6 of Fassberg's exemplified compositions contain ethanol. Thus, an ordinary skilled artisan would likely choose both oleic acid and ethanol from the list of preferred excipients and surfactants from which to prepare pharmaceutical aerosol suspension formulations. An ordinary skilled artisan would have had a reasonable expectation of successfully formulating suspension formulations of formoterol and ciclesonide containing ethanol and/or oleic acid, because Fassberg taught that suspension formulations could contain surfactants and/or excipients, such as ethanol.

Regarding the amount of ethanol and oleic acid recited in Appellants' claims, this amount overlaps with the amounts taught as being suitable by Fassberg. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(V) Claims 2, 4, 7-8, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gavin et al. (WO 01/78738) ("Gavin") in view of Calatayud et al. (U.S.

Patent No. 5,482,934) (IDS) as applied to claims 1, 3, 9, and 11 above, and further in view of Keller et al. (WO 00/07567) (IDS)[1], wherein U.S. Patent No. 6,475,467 (Keller) (IDS) is being used as the English language equivalent of WO 00/07567**.**

Appellant Claims

Appellants claim a composition as described above, further comprising disodium chromoglycate in a non-therapeutically and/or non-prophylactically active concentration, and, in some embodiments, ethanol and/or a surfactant (e.g. oleic acid).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Gavin's teachings are set forth above. The teachings of Calatayud are set forth above.

Keller teaches that the inclusion of solid salts of cromoglycic acid and/or nedocromil as a vehicle at non-therapeutically or non-prophylactically effective concentrations improves the dispersion characteristics and the chemical and physical stability or active ingredients which are sensitive to moisture and are present in pharmaceutical aerosol suspension formulations (abstract). Particularly preferred carrier materials are disodium cromoglycate and nedocromil sodium (col. 6, lines 32-36). Suitable active agents used in combination with disodium cromoglycate or nedocromil sodium are any that which can be administered as suspended aerosols in therapeutically effective amounts, such as formoterol, formoterol fumarate, and ciclesonide (col. 5, lines 13-29). The aerosol formulations may also contain a combination of

[1] Appellants' March 7, 2006 IDS indicated that U.S. Patent No. 6,475,467 is the English language equivalent of WO 00/07567 (i.e. "corresponds to…").

active agents, such as formoterol or a pharmaceutically acceptable derivative, and ciclesonide (col. 5, lines 36-47).

Keller's compositions do not require the addition of cosolvents or surfactants; however, if a cosolvent and/or surfactant are desired these may be included (col. 4, line 66 through col. 5, line 7 and col. 8, line 59 through col. 9, line 28). Preferred cosolvents, if present, include ethanol (col. 9, lines 4-5). The amount of cosolvent present is not over about 15% w/w, preferably not over about 10%, usually not over about 5% w/w (col. 9, lines 8-13). Suitable surfactants, if present, include oleic acid, and are generally present in an amount ranging from 0.001 to 0.1% w/w (col. 9, lines 14-28). Keller exemplifies the preparation of an aerosol suspension formulation comprising (i) ~99.93% w/w HFA 227, (ii) ~0.007% w/w of formoterol fumarate, (iii) ~0.014% of disodium cromoglycate, and (iv) ~0.043% of fluticasone propionate in Example 6 (col. 10, lines 50-63).

Keller specifically states that the inclusion of disodium cromoglycate or nedocromil sodium to formulations can be used to stabilize moisture-sensitive compounds, such as formoterol fumarate (col. 4, lines 51-59) as well as to reduce the tendency to adhesion of electrostatically charged active compounds, such as micronized corticosteroids (col. 4, lines 60-65).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Gavin lacks the teaching of formulations comprising (i) disodium cromoglycate in a sub-therapeutic amount and (ii) ethanol and/or a surfactant. This deficiency is cured by the teachings of Keller.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious at the time of Appellants' invention to combine the teachings of Gavin and Keller, because both references teach inhalable formulations comprising anti-inflammatory steroids and/or formoterol fumarate that can be formulated as aerosols suspensions with hydrofluorocarbon propellants (e.g. HFA 227). An ordinary skilled artisan would have been motivated to modify the teachings of Gavin to include disodium cromoglycate to obtain suspension formulations exhibiting improved physical and chemical stability (Keller). Furthermore, an ordinary skilled artisan would have been motivated to include ethanol and or a surfactant, such as oleic acid, because Keller teaches that both ethanol and surfactants can be added to the suspension formulation and specifies suitable amounts of cosolvent and surfactants that can be added if desired. An ordinary skilled artisan would have had a reasonable expectation of combining the teachings of Gavin and Keller, because both references teach HFA-based pharmaceutical suspensions and Keller teaches amounts of disodium cromoglycate as well as amounts of ethanol and oleic acid, if present, that can be suitably co-formulated with compositions comprising medicaments, such as formoterol fumarate and a corticosteroid.

Regarding the amount of ethanol recited in Appellants' claims, this amount overlaps with the amounts taught as being suitable by Keller. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

B. Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6 of copending Application No. 10/537,356 (copending '356) in view of Burt (US 2002/0030068) and Aberg et al. (U.S. Patent No. 5,795,564) (IDS).[2]

Claim 1 of the instant application has been described above. Independent claim 6 of copending '356 claims a formulation comprising R,R-formoterol and ciclesonide in a form administrable from a dry powder inhaler. The difference between claim 1 of the instant application and claim 6 of copending '356 is that the composition of the instant application is a suspension formulation (i.e. it comprises insoluble particulate formoterol and particulate ciclesonide) and claim 1 of the instant application does not specify that formoterol is (R,R)-

formoterol. Regarding (R,R)-formoterol, the use of this enantiomer is prima facie obvious at the time of the instantly claimed invention, because it was known to be the broncho-active enantiomer of the commercially available racemic formoterol mixture (Aberg). Regarding conversion of a mixture of particulate formoterol and ciclesonide into a suspension, this requires the mere addition of HFA propellant, which can be done by various well known procedures (e.g. cold filling of the propellant into a metered dose inhaler pre-filled with a particulate mixture). Furthermore, inhalable aerosol suspensions are one of the conventionally used inhalable formulations (i.e. (i) inhalable aerosol solutions, (ii) inhalable aerosol suspensions, (iii) propellant-free solutions, (iv) propellant-free suspensions, and (v) inhalable powders). Aerosol suspensions comprising a mixture of a beta2-agonist with an anti-inflammatory steroid are well known (Burt). Therefore, a person of ordinary skill in the art at the time of the instant invention would have found claims 1 and 5 *prima facie* obvious over claim 6 of copending Application No. 10/537,356 (copending '356) in view of Burt (US 2002/0030068) and Aberg et al. (U.S. Patent No. 5,795,564) (IDS).

This is an obviousness-type double patenting rejection.

(10) Response to Argument

(IA) Appellants have traversed this rejection by attacking the references individually, identifying what elements each reference alone does not teach, and arguing that (1) allegedly none of the cited references when taken alone or in combination teach or fairly suggest all the elements of the claimed invention; (2) allegedly there is no motivation to obtain the alleged

[2] Copending Application No. 10/537,356 ("copending '356") issued as U.S. Patent No. 7,879,833 B2 ("USPN 833")

missing elements from teachings of the cited references; and (3) allegedly the combined teachings would not have motivated the ordinary skilled artisan to prepare the presently claimed subject matter.

The Examiner respectfully disagrees with Appellants' traversal arguments. In response to Appellants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Appellants' arguments essentially are based on the premise that because Aberg does not anticipate the claims and Burt, Garcia, and Calatayud individually do not cure Aberg's deficiencies that the rejection must be improper. This premise is flawed, because it assumes that the citation of multiple references renders a rejection improper and does not properly consider what the combined prior art references teach collectively. In response to Appellants' implied argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). Appellants arguments only specifically address the combined teachings of the cited prior art at page 14 of the Appeal brief, wherein Appellants allege they have not conducted a piece meal analysis and conclude that the combined teachings would not have motivated the ordinary skilled artisan to prepare the presently claimed subject matter.

Appellants' arguments are found unpersuasive for the reasons of record as further explained below. The secondary references cited establish that it was well known in the art that

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on February 1, 2011. Claim 6 of copending '356 corresponds to claim 1 of USPN '833 as amended in the notice of

(i) chlorofluorocarbons were being phased out in favor of propellants, such as hydrofluorocarbons (HFAs or HFCs), which were not damaging to the ozone layer (Burt); (ii) HFA suspension formulations comprising the combination of a betamimetic bronchodilator (*e.g.* formoterol) and an anti-inflammatory steroid (e.g. budesonide) were known or fairly suggested (Burt and Garcia); (iii) the combination of an inhaled corticosteroid (*e.g.* budesonide) and an inhaled beta-2 adrenergic bronchodilator (*e.g.* formoterol) were known to be as effective as administration of a much higher dose of corticosteroid alone (Garcia); and (iv) ciclesonide is a more desirable anti-inflammatory steroid, than budesonide and other commonly administered anti-inflammatory steroids, because it has a higher therapeutic index. Thus, the ordinary skilled artisan would clearly have been motivated with a reasonable expectation of success to replace the CFC propellants taught by Aberg with suitable alternative propellants such as HFA's, because CFC's were being phased out. An ordinary skilled artisan knowing that the combination of an inhaled corticosteroid and an inhaled betamimetic bronchodilator (*e.g.* formoterol) is as effective as a higher dose of inhaled corticosteroid, would have been motivated to modify Aberg to include inhalable corticosteroids (Garcia), especially given that the prior art had explicitly taught/suggested the combination of bronchodilating betamimetics and anti-inflammatory steroids in HFA suspension formulations. The ordinary skilled artisan would have been motivated to select ciclesonide as the corticosteroid added to Aberg's formulation and not utilize other corticosteroids or to substitute ciclesonide for other corticosteroids, because ciclesonide exhibits a desirable higher therapeutic index compared to other corticosteroids typically administered by inhalation. It is also noted that Aberg explicitly states that (R,R)-formoterol

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allowance mailed on September 23, 2010. This rejection is no longer provisional.

may be combined with additional therapeutic agents at column 10, lines 36-40. Thus, for the aforementioned reasons there is ample motivation to modify the teachings of Aberg to utilize HFA propellants, include anti-inflammatory steroids (*i.e.* an additional therapeutic agent), and select ciclesonide as the anti-inflammatory steroid. The rejection is maintained.

Regarding the recitation in Appellants' claims that the claimed suspension formulations exhibit the property of being readily dispersible and that upon the use of the claimed suspension by redispersion, the suspension does not flocculate to prevent reproduction of dosing of the first and/or second active ingredients, the Examiner notes that the cited prior art strongly suggests the combination of the same recited compositions components. In fact, the prior art contains disclosures of viable pharmaceutical aerosol suspensions (*i.e.* dispersions) (*e.g.* Fassberg). Moreover, Appellants identify in their specification at page 2 several prior art references that disclose readily dispersible HFA suspension formulations. Thus, there is no evidence of record that the particular components resulting from the combined teachings of the cited prior art are not dispersible, would be expected by the ordinary skilled artisan not to be dispersible or re-dispersible, or that the ordinary skilled artisan would reasonably expect the composition resulting from the cited prior art teachings would be expected to exhibit problems with flocculation causing inconsistent dosing. The rejection is maintained. It is respectfully requested that the Board of Patent Appeals and Interferences (BPAI) affirm the instant rejection.

(IIA) Appellants have traversed this rejection by reiterating their traversal arguments regarding the first Aberg rejection, attacking the Fassberg reference individually, and stating that Fassberg fails to cure the alleged deficiencies of Aberg, Burt, García-Marcos, and Calatayud.

The Office's rebuttal of Appellants' traversal arguments with regards to rejection (IA) is herein incorporated by reference. The rejection is maintained and it is respectfully requested that the BPAI affirm the instant rejection.

(IIIA) Appellants have traversed this rejection by (1) reiterating their arguments traversing the first Aberg rejection, (2) attacking all the references individually including Gavin, and (3) alleging that Gavin is an improper reference because it discloses the combination of R,R-formoterol and rofleponide – a corticosteroid- and does not disclose Appellants' claimed invention comprising the combination of R,R-formoterol and ciclesonide. Appellants' arguments emphasize that Gavin -in isolation from the teachings of Calatayud- teaches rofleponide and not ciclesonide.

The Examiner respectfully disagrees with Appellants' traversal arguments. The Office's rebuttal of Appellants' traversal arguments presented regarding the first Aberg rejection as it pertains to the instant rejection are herein incorporated by reference. In response to Appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Appellants' arguments essentially are based on the premise that because Gavin does not anticipate the claims the rejection must be improper. This line of reasoning is flawed, because the instant rejection is not based on an anticipation analysis, but rather an obviousness analysis and using the combination of two prior art references. Regarding (3), the teachings of the combined prior art provide strong motivation to substitute the

rofleponide in Gavin's invented compositions for ciclesonide and obtain the claimed composition, because of the prior-art recognized higher therapeutic index of ciclesonide compared to other inhaled corticosteroids. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. Appellants' arguments are unpersuasive. The rejection is maintained and it is respectfully requested that the BPAI affirm the instant rejection.

(IVA) Appellants have traversed this rejection by reiterating their traversal arguments regarding the first Gavin rejection. The Office's rebuttal of Appellants' traversal arguments from section (IIIA) is herein incorporated by reference. The rejection is maintained and it is respectfully requested that the BPAI affirm the instant rejection.

(VA) Appellants have traversed this rejection by reiterating their traversal arguments regarding the first Gavin rejection. The Office's rebuttal of Appellants' traversal arguments from section (IIIA) is herein incorporated by reference. The rejection is maintained and it is respectfully requested that the BPAI affirm the instant rejection.

(B) Appellants traverse this rejection for the first time during the prosecution history of this application by reproducing claim 1 of the instant application and claim 6 [sic] of U.S. Patent No. 7,879,833 (formerly copending Application No. 10/537,356) and stating without any substantive analysis that the two claims represent clearly divergent scopes and that issuance of

claim 1 of the instant application would not be an unjustified or improper timewise extension of the right to exclude of claim 6 [sic] of the '833 patent.

The Examiner respectfully finds Appellants' traversal arguments unpersuasive. Firstly, it is noted that Appellants incorrectly refer to claim 6 of U.S. Patent No. 7,879,833 (USPN '833). Whereas it is correct that the previously provisional rejection over copending Application No. 10/537,356 was over claim 6, when copending '356 issued as USPN '833, claim 6 was renumbered as claim 1 in the issued patent. Thus, Appellants' arguments are understood to refer to claim 1 of USPN '833 and not to claim 6 of USPN '833.

Regarding Appellants' arguments, both claim 1 of the instant application and claim 1 of USPN '833 recite pharmaceutical compositions that contain solid particles of ciclesonide and R,R-formoterol as the sole therapeutic active agents. In USPN '833 the composition is in the form of a powder (*i.e.* solid particles), whereas in claim 1 of the instant application the suspended particles of ciclesonide and R,R-formoterol are understood to refer to solid particles suspended in the propellant. The instant rejection acknowledges that claim 1 of USPN '833 (formerly claim 6 of copending '356) does not recite a propellant and cures this deficiency by the citation of Burt (US 2002/0030068) (of record) and Aberg (U.S. Patent No. 5,795,564) (IDS). Appellants' arguments do not address the cited teachings of Burt and Aberg. Appellants do not meaningfully address the assertion that it would be a prima facie obvious modification of claim 1 of USPN '833 in view of the teachings of Burt and Aberg to prepare suspension formulations by the addition of a conventional pharmaceutically acceptable hydrofluorocarbon propellants (*e.g.* 1,1,1,2-tetrafluoroethane). Thus, Appellants' arguments are found unpersuasive. The rejection is maintained and it is respectfully requested that the BPAI affirm the instant rejection.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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